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The co-occurrence of autism spectrum disorder and attention-deficit/hyperactivity disorder symptoms in parents of children with ASD or ASD with ADHD

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Background: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) share about 50–72% of their genetic factors, which is the most likely explanation for their frequent co-occurrence within the same patient or family. An additional or alternative explanation for the co-occurrence may be (cross-)assortative mating, e.g., the tendency to choose a partner that is similar or dissimilar to oneself. Another issue is that of parent-of-origin effect which refers to the possibility of parents differing in the relative quantity of risk factors they transmit to the offspring. The current study sets out to examine (cross-)assortative mating and (cross-)parent-of-origin effects of ASD and ADHD in parents of children with either ASD or ASD with ADHD diagnosis. **Methods:** In total, 121 families were recruited in an ongoing autism-ADHD family genetics project. Participating families consisted of parents and at least one child aged between 2 and 20 years, with either autistic disorder, Asperger disorder or PDD-NOS, and one or more biological siblings. All children and parents were carefully screened for the presence of ASD and ADHD. **Results:** No correlations were found between maternal and paternal ASD and ADHD symptoms. Parental ASD and ADHD symptoms were predictive for similar symptoms in the offspring, but with maternal hyperactive-impulsive symptoms, but not paternal symptoms, predicting similar symptoms in daughters. ASD pathology in the parents was not predictive for ADHD pathology in the offspring, but mother's ADHD pathology was predictive for offspring ASD pathology even when corrected for maternal ASD pathology. **Conclusions:** Cross-assortative mating for ASD and ADHD does not form an explanation for the frequent co-occurrence of these disorders within families. Given that parental ADHD is predictive of offspring' ASD but not vice versa, risk factors underlying ASD may overlap to a larger degree with risk factors underlying ADHD than vice versa. However, future research is needed to clarify this issue. **Keywords:** Assortative mating, parent-of-origin effect, autism spectrum disorder, attention-deficit/hyperactivity disorder.

Introduction

The classical prototypes of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) seem to provide outstanding examples of disorders that are so incompatible in their manifestation that they cannot co-occur. Based on their *DSM-IV* diagnostic criteria (APA, 2000), ASD and ADHD indeed have little in common. ASD has a prevalence of around 1% in children and is defined by impaired communication and social interaction skills, as well as repetitive and restricted behavior and interests (APA, 2000; Fombonne, 2009), whereas ADHD has a prevalence of around 5% in children and is defined by severe inattention, hyperactivity and impulsivity (APA, 2000; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). The diagnostic guidelines in the *DSM-IV* have so far prevented making a comorbid diagnosis, based on the rationale that ADHD symptoms in patients with ASD are primarily attributable to the ASD diagnosis. As a result, over the past decades, ASD and ADHD have been studied in isolation from each other, each disorder within its research tradition, networks of collaborating experts and theoretical frameworks, without too much cross-fertilization. However, recent studies using clinical samples indicate that 22–83% of children with ASD have symptoms that satisfy DSM-IV criteria for ADHD (e.g., Frazier et al., 2001; Lee & Ousley, 2006; Rowlandson & Smith, 2009; Sinzig, Walter, & Doepfner, 2009). Vice versa, 30–65% of children with ADHD have clinically significant symptoms of ASD (Clark,

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Feehan, Tinline, & Vostanis, 1999; Santosh & Mijovic, 2004). A population-based study used the ADI-R and the ADOS-G to confer an ASD diagnosis, and the Child and Adolescent Psychiatric Assessment (CAPA) structured interview to establish an ADHD diagnosis, and reported that 28.2% of children with ASD have co-occurring ADHD (Simonoff et al., 2008). A population-based twin study classified suspected children as having ASD using the Diagnostic and Wellbeing Assessment (DAWBA) and classified suspected ADHD by setting a cut-off on the Revised Conners' Parent Rating Scale (CPRS-R). This twin study reported that 41% of children with ASD had co-occurring ADHD, and 22% of children with ADHD had co-occuring ASD (Ronald, Simonoff, Kuntsi, Asherton, & Plomin, 2008). With *DSM-5* on its way (see draft criteria at http://www.dsm5.org), wherein the presence of autistic disorder (the proposed new name for ASD) no longer excludes a diagnosis of ADHD, it is likely that this situation will boost research on the shared pathophysiology of ASD and ADHD.

Examination of a shared pathophysiology of ASD and ADHD up to now has already shown that the two disorders share very similar structural and functional brain abnormalities (see for a review Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). Furthermore, recent family and twin studies provide support for the hypothesis that ASD and ADHD originate from partly similar familial/genetic factors (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010). Both disorders are highly heritable (ASD >90% and ADHD about 76% (Freitag, 2007; Pamploma et al., 2009)) and about 50–72% of the contributing genetic factors overlap between ASD and ADHD. These shared genetic and neurobiological underpinnings form an explanation why both disorders occur so frequently within the same patient and family.

An intriguing, but virtually uninvestigated, additional explanation for the frequent co-occurrence of ASD and ADHD is that (cross-)assortative mating may occur in the parents of children with these disorders. Assortative mating is a term used to describe one's tendency to (not randomly) choose a partner that is either similar or dissimilar from oneself in a variety of traits, such as age, education, personality or religion (Vandenberg, 1972). It may be, for example, that adults with ASD traits attract spouses with ADHD traits or vice versa. Though studies were unable to find support for assortative mating regarding ASD (Hoekstra, Bartels, Verweij, & Boomsma, 2007) and only found some evidence for ADHD (Boomsma et al., 2010), the possibility of cross-assortative mating for ASD and ADHD has not yet been examined. Such cross-assortative mating has been described for certain other psychiatric disorders, such as affective disorders and conduct problems (Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005) and for alcoholism, generalized anxiety disorders, panic disorder and phobias (Maes et al., 1998). If present, cross-assortative mating may result in a 'double-whammy' effect with respect to risk genes segregating to the offspring: two separate sets of risk genes, an ASD and ADHD set, one from each parent, are inherited together, resulting in the co-occurrence of ASD and ADHD in the offspring.

Another issue that deserves further attention in the symptom transmission of ASD and ADHD is whether parents differ in the relative quantity of risk factors they transmit to the offspring. This is also known as parent-of-origin effect. If present, it could imply that the effect of a risk allele depends on whether it originates from the mother or father. Absence of parent-of-origin effect indicates that the risk allele is more or less equally transmitted from mothers and fathers to the offspring. For both ASD and ADHD mixed findings of parent-of-origin effects have been documented. Some studies reported that both disorders were mainly transmitted through the maternal line (Arking et al., 2008; Banerjee et al., 2006; Lauritsen, Pedersen, & Mortensen, 2005), other studies reported the opposite (Anney et al., 2008; Fradin et al., 2010; Goos, Crosbie, Payne, & Schachar, 2009; Hawi et al., 2010) and a few found no evidence for parent-of-origin effects (Goos, Ezzatian, & Schachar, 2007; Kim et al., 2007). To the authors' knowledge, thus far, no studies have focused on the cross-parent-of-origin effects of ASD and ADHD, i.e., whether it matters if fathers or mothers have ADHD symptoms for the children's risk of also developing ASD next to ADHD. This may be influenced by the child's gender as well, as suggested by two previous studies showing that girls may be more susceptible to the inheritance of ADHD through either parent (Hawi et al., 2005) or only the maternal line (Goos et al., 2007). The parent-of-origin effects may also be influenced by different inheritance patterns of the two symptom domains of ADHD, e.g., inattentive versus hyperactive-impulsive symptoms (Nikolas & Burt, 2010).

It is clear that the relationship of ASD and ADHD pathology between parents deserves further attention, as well as possible parent-of-origin effects in the transmission of ASD and ADHD symptoms to the offspring. Therefore, the current study sets out to examine these issues in 121 families in which at least one child was affected with ASD and at least one additional biological sibling was available for analyses. Self-reported ASD and ADHD symptoms were obtained from the parents and were related to each other and their offspring ASD and ADHD symptoms.

Methods

Participants

Families were recruited as part of an ongoing family genetics project [Biological Origins of Autism (BOA)]. The BOA project aims to examine the genetic, biochemical and cognitive origins of ASD and, in addition, study the overlap between ASD and ADHD on these

levels. Families were included in the current study if at least one child between 2 and 20 years old, with either an autistic disorder, Asperger disorder or PDD-NOS (proband), at least one biological sibling (regardless of possible ASD-status) and at least one biological parent wanting to participate. All families had to be of European Caucasian descent. Exclusion criteria for the probands and siblings were epilepsy, a diagnosis of a defined genetic or non-genetic cause of ASD (Rett's syndrome, fragile X syndrome) or a genetic disease such as Down-syndrome. Comorbid *DSM-IV* disorders were not excluded.

All children were screened with the Social Communication Questionnaire (SCQ) (Rutter et al., 2003) completed by parents and teachers. Even though the SCQ has not been studied and validated as an instrument for teachers, we use also the teachers report as screenings method, to avoid missing any actual case. Families were included if at least one child presented a score above 10 on the parent version (to avoid the exclusion of children with milder ASD symptoms e.g., false negatives) or above 15 on the teacher version of the SCQ. We chose a higher cutoff for the teacher than for the parent reported SCQ because teachers often reported more subtle ASD symptoms that were not confirmed by parents' SCQ reports or the administered Autism Diagnostic Interview Revised (ADI-R) to parents. For all children scoring above the cut-off, a formal diagnosis of ASD was made by a certified clinician using the Autism Diagnostic Interview-revised (ADI-R) (Le Couteur, Lord, & Rutter, 2003). The protocol for screening and measuring ADHD was similar to the protocol used in the International Multicenter ADHD Genetics (IMAGE) study (Brookes et al., 2006). In short, the Conners long version Rating Scales-Revised (CRS-R) (Conners, 1997) completed by parents and teachers was used for screening for ADHD. Participants of 18 years and older filled out the Conners Adult Rating Scales-Self-report: Long version (CAARS-S:L). A T-score ≥63 on one of the ADHD-subscales of the CRS-R (parent or teacher) or CAARS was considered clinical. For all children scoring above cut-off and/or having a previous clinical diagnosis of ADHD, the parental account for childhood symptoms (PACS) (Taylor, Sandberg, Thorley, & Giles, 1991) was administered by a certified clinician to obtain a diagnosis of ADHD.

We were able to enroll 121 families in this study, see Table 1 for the descriptive characteristics. Due to the study-design, all probands had a diagnosis of ASD and there were no children with a pure ADHD diagnosis in this group. In total, 38.8% of the probands with ASD also fulfilled criteria for ADHD. Of the 184 siblings, 15.6% had pure ASD, 9.4% pure ADHD, and 5.4% had ASD and ADHD. Both fathers and mothers scored above population average with respect to self-reported ASD symptoms. The mean scores of ADHD inattentive symptoms of parents were comparable to the norm, however, the mean ADHD hyperactive-impulsive symptoms were significantly lower than the mean scores of the general population.

Instruments

Self-reported ASD symptoms of parents and parent-reported ASD symptoms in children were measured using the child and adult version of the autism spectrum quotient (AQ) (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). These questionnaires have been found reliable and valid (Auyeung, Baron-Cohen, Wheelwright, & Allison, 2008; Hoekstra, Bartels, Cath, & Boomsma, 2008) and have the advantage that the parent and child versions are directly comparable. The questionnaires consists of 50 items rated on a 4-point scale. Total scores for children and parents were obtained by summing up all items, resulting in a score between 50 and 200 (Hoekstra et al., 2008, 2007). The ASD symptom scores were treated on the same dimension, because the AQ has not been designed to differentiate between ASD symptom classifications. Self-reported ADHD symptoms of parents and adult children (18 years and older) were measured with the CAARS-S:L (Conners, Erhardt, & Sparrow, 1998, 1999). The *DSM-IV* ADHD subscales were used to operationalize inattentive and hyperactive-impulsive symptoms of parents. For children of 18 years and older, the scaled scores were averaged across raters (self-report and parent-report). For offspring below the age of 18 years, parent and teacher reports on the CRS-R (Conners, 1997) were averaged. If no teacher report was present (N = 23, 7.5%), only the parent report was used.

Procedure

Families potentially satisfying inclusion criteria registered at an outpatient clinic specialized in ASD and ADHD pathology (Karakter Child and Adolescent Psychiatry University Center) and members of the Dutch Autism Association (NVA) received a brochure containing information regarding the study and were requested to return a pre-stamped response card. A short telephone screening and, subsequently, screening questionnaires were used to verify if families could participate. Those families were invited to visit the clinic, where a trained researcher conducted the ADI-R and the PACS. Additional data collected included blood samples of all family members and neuropsychological data of the children. The study was approved by the local medical ethics board and parents and children (12 years and older) signed for informed consent.

Data-analyses

Analyses were performed with Statistical Package for the Social Science version 16 (SPSS 16; IBM Corporation, Armonk, NY, USA). Less than 5% of child data, <7% of father data and <2% of mother data was missing and we used the expectation maximization algorithm (Dempster, Laird, & Rubin, 1977) to impute the missing values. The AQ and Conners data for parents and children were transformed into z-scores to depict the measures on the same scale using the age- and sex-specific means and SDs for these questionnaires (Hoekstra et al., 2008, 2007; Saviouk et al., 2011). Thereafter, because the distribution of scores was not completely normal, the variables were normalized using the Van der Waerden transformation (SPSS 16; IBM Corporation).

To examine the presence of (cross-)assortative mating, Pearson correlation analyses with the AQ and CAARS z-scores were performed to examine whether

Table 1 Characteristics of the participants

	(1) Fathers $N = 121$		(2) Mothers $N = 121$		(3) Population parents		*t*-test	(4) probands $N = 121$		(5) Siblings $N = 184$		(6) Population children		*t*-test
	M	*SD*	*M*	*SD*	*M*	*SD*	Contrast	*M*	*SD*	*M*	*SD*	*M*	*SD*	Contrast
% Male								85.1		49.5				
Age in years	45.8	5.8	43.0	5.3				11.7	3.7	11.4	4.7			4 = 5
Education	4.5[a]	1.0	4.4[a]	0.87	4.3[b]		1 & 2 = 3							
Social Communication Questionnaire								19.9	8.0	6.4	7.2	4.7[c]	5.0[c]	4 > 6 and 5 = 6
Autism quotient	115.5	18.6	109.1	22.2	♀102.9 ♂105.7[d]	♀11.5 ♂11.0[d]	1 & 2 > 3	138.1	17.8	113.3	24.6	♀ 100.8 ♂104.0[e]	10.5[e]	4 > 6 and 5 = 6
Conners inattentive scores	5.8	4.7	4.6	5.3	♂ 5.3 ♀ 5.3[f]	♀ 3.2 ♂ 3.1	1 & 2 = 3	59.7	9.9	53.2	9.8	50.0	10.0	4 & 5 > 6
% Above cut-off T >63	4.1		4.1		♀ 6.8 ♀ 7.4[g]		1 & 2 = 3	38.0		16.3		12		4 > 6 and 5 = 6
Conners hyperactive scores	5.4	3.7	5.1	4.1	♂ 6.7 ♀ 7.0[f]	♀ 3.3 ♂ 2.9	1 & 2 < 3	61.8	11.3	53.3	10.6	50.0	10.0	4 & 5 > 6
% Above cut-off T >63	4.1		4.1		♀ 6.8 ♀ 7.4[g]		1 & 2 = 3	43.8		16.8		12		4 > 6 and 5 = 6
% ASD (ADI)[h]														
Autism								59.5		6.1				
Asperger								3.3		0.7				
PDD-NOS								37.2		8.8				
% ADHD (PACS)[i]														
Inattentive subtype								15.7		5.1				
Hyperactive subtype								9.9		1.4				
Combined subtype								13.2		2.9				
% Total ADHD only								–		9.4				
% Total ASD + ADHD								38.8		5.4		5		4 & 5 > 6

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; PACS, parental account for childhood symptoms.
[a]1 = nursery school 2 = primary education 3 = secondary education, first phase 4 = secondary education, second phase 5 = higher education, first phase 6 = higher education, second phase 7 = higher education, third phase.
[b]Central Bureau of statistics (CBS) 2009.
[c]Based on population cohort study ($N = 247$) (Chandler et al., 2007).
[d]Based on Dutch population-based sample ($N = 302$) (Hoekstra et al., 2008).
[e]Based on Dutch population-based sample of twins ($N = 464$) (Hoekstra et al., 2007).
[f]Norms from the Dutch Twin register.
[g]Based on epidemiology study ($N = 12.000$) (Boomsma et al., 2010).
[h]Measured with the autism diagnostic interview (ADI-R).
[i]Measured with the Parental Account for Childhood Symptoms (PACS).

symptoms within and between parents were correlated. To examine the presence of parent-of-origin effects, generalized estimation equations (GEE) with an exchangeable working correlation matrix (all measurements were equally correlated), scale parameter method on deviance and robust estimators were used. Family number was used as subject effect to account for clustered data. This allowed us to evaluate the relationship between parental and offspring symptoms but with correction of clustered data (i.e., multiple parent-offspring correlations were calculated per family). GEE-analyses are a convenient and general approach to analyze clustered (family) data (Liang & Zeger, 1986). Predictors were sex and age of the child, parents' age, parents' symptoms, and the two-way interactions between parental pathology and sex or age of the parent. Dependent variable was the child's symptoms. When the two-way interactions (between parental pathology and sex or age of the parent) were non-significant, these were dropped from the model and the model was rerun. The model was run separately for ADHD symptoms within families, ASD symptoms within families, and lastly for the relationship between parental ASD and offspring ADHD symptoms and vice versa. In the latter two analyses, when a significant effect of parental ASD on offspring ADHD symptoms was found, the model was rerun with parental ADHD symptoms added to the model to examine whether the observed effect was partially accounted for by parental ADHD pathology. The same procedure was undertaken for the relationship between parental ADHD and offspring ASD symptoms. For all analyses correction for multiple testing using the 95% CI, was performed using the False Discovery Rate procedure (Benjamini, 2010).

Results

The relationship between ASD and ADHD pathology within and between parents

Within both fathers and mothers significant positive correlations were found between their ASD and ADHD symptom scores (Table 2). No significant correlations were found between maternal and paternal ASD and ADHD symptoms.

Preferential parental transmission

Because there were no significant correlations between maternal and paternal pathology, GEE analyses could be conducted with maternal and paternal pathology as predictors in the same model. For ASD pathology, an equally strong relationship between both paternal and maternal and offspring ASD symptoms was found, regardless of the child's sex or parents' age (see Table 3 and Figure 1). No parent-of-origin effects were found for ADHD inattentive pathology, although only maternal inattentive symptoms survived correction for multiple testing and predicted both inattentive and hyperactive-impulsive symptoms in offspring regardless of the sex and age of the child. A parent-of-origin effect was present for parental hyperactive-impulsive symptoms, with maternal (but not paternal) symptoms being predictive for daughters' hyperactive-impulsive symptoms. Maternal or paternal hyperactive-impulsive symptoms were not related to hyperactive-impulsive symptoms in sons or offspring inattentive symptoms. Parents reported both on their own symptoms and on the symptoms of their children. To correct for a possible bias, we repeated our analyses with only the teacher score (only available for the ADHD symptoms) as the dependent variable. Doing so, we found that all results were in the same direction as before, but no longer significant (maternal inattentive symptoms with child hyperactive- impulsive symptoms $B = .02$, $p = 0.79$, maternal inattentive symptoms with child inattentive symptoms $B = .02$, $p = 0.84$, and maternal hyperactive- impulsive symptoms with daughters hyperactive- impulsive symptoms $B = .09$, $p = 0.37$).

Cross-disorder analyses revealed no significant relationship between parental ASD and offspring ADHD symptoms (See Figure 2). Vice versa, a relationship was found moderated by parent-of-origin effects. Maternal, but not paternal, ADHD inattentive and hyperactive-impulsive symptoms were predictive of daughters' ASD symptoms, but only for the

Table 2 Correlations of self reported ASD and ADHD symptoms between and within parents

	Father			Mother		
	ASD[b]	ADHD inatt[c]	ADHD hyp-imp[d]	ASD[b]	ADHD inatt[c]	ADHD hyp-imp[d]
Father						
ASD	1	.48[a]	.43[a]	.00	.01	.05
ADHD inatt		1	.51[a]	−.11	.02	.07
ADHD hyp-imp			1	−.01	−.08	.02
Mother						
ASD				1		
ADHD inatt				.37[a]	1	
ADHD hyp-imp				.28[a]	.58[a]	1

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.
[a]Correlation is significant at the 0.01 level and after correction for multiple testing.
[b]ASD symptoms measured with the autism quotient (AQ).
[c]ADHD inattentive symptoms measured with the Conners' Adult Rating Scales- Self-report: Long version (CAARS-S:L).
[d]ADHD hyperactive-impulsivity symptoms measured with the Conners' Adult rating Scales- Self-report: Long version (CAARS-S:L).

Table 3 Parent-of-origin effects of ASD and ADHD symptoms to the offspring (*z*-scores)

	Child ASD[a]	*p*-value	Parent-of-origin effect	Child ADHD inatt	*p*-value	Parent-of-origin effect	Child ADHD hyp-imp	*p*-value	Parent-of-origin effect
Father/mother									
ASD[b]	**.16/.15**	**.001/.01**	No (p = .61)	.13/.01	.04/.87	No (p = .20)	.10/.03	.11/.59	No (p = .41)
ADHD inatt[c]	♂ .02/♂ .03	♂.88/♂ .16	No (p = .75)	.08/**.15**	.79/**.02**	No (p = .53)	.05/**.16**	.49/**.01**	No (p = .30)
	♀ .17/♀ **.30**	♀ .26/♀ **.001**	No (p = .46)						
ADHD hyp-imp[d]	♂ .08/♂ –.08	♂.33/♂ .11	No (p = .11)	.07/.13	.36/.07	No (p = .53)	♂ .03/♂.07	♂ .11/♂ .29	No (p = .75)
	♀ –.02/♀ **.35**	♀ .94/♀ **.001**	**Yes (p = .03)**				♀ .03/♀**.32**	♀ .24/♀ **.001**	**Yes (p = .03)**

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.
Findings in bold are significant after correction for multiple testing.
[a]Regression weights are not specified for gender, unless significant gender-interaction effects were found.
[b]ASD symptoms measured with the autism quotient (AQ).
[c]ADHD inattentive scores measured with the Conners' long version Rating Scales Revised (CRS-R).
[d]ADHD hyperactive-impulsivity scores measured with the Conners' long version Rating Scales Revised (CRS-R).

latter we found a significant parent-of-origin effect. Adding maternal ASD symptoms to the model did not change this effect. For the hyperactive-impulsive symptoms in mothers and daughters, an interaction of mother's age was observed. Offspring ASD symptoms were related to the hyperactive-impulsive symptoms of younger mothers (p = .007), but not of older mothers (p = 0.14) when using a median split on mother's age.

Discussion

In the current study we set out to examine cross-assortative mating and (cross-)parent-of-origin effects of ASD and ADHD symptoms in parents and children to shed more light on the frequent co-occurrence of both disorders within patients and families. No correlations were found between maternal and paternal ASD and ADHD symptoms, making (cross-)assortative mating unlikely in our sample. An equally strong relationship between paternal, maternal and offspring ASD symptoms was found, regardless of the child's sex or parents' age. Concerning ADHD, no parent-of-origin effects were found for ADHD inattentive pathology, although only maternal inattentive symptoms survived correction for multiple testing and predicted both inattentive and hyperactive-impulsive symptoms in offspring regardless of the sex and age of the child. A parent-of-origin effect was present for parental hyperactive-impulsive symptoms, with maternal (but not paternal) symptoms being predictive for daughters' hyperactive-impulsive symptoms. Parental ASD pathology was not predictive for offspring ADHD pathology, but mother's ADHD pathology was predictive for offspring ASD pathology even when corrected for maternal ASD pathology.

Our findings of moderate to strong relationships between parental and offspring symptoms are in line with previous studies (for example, Fradin et al., 2010; Hawi et al., 2010). The result that both paternal and maternal ASD symptoms are equally strongly related to offspring ASD symptoms, concurs with the findings from recent studies (Arking et al., 2008; Banerjee et al., 2006; Lauritsen et al., 2005) and contradicts hypotheses that ASD pathology is mainly transmitted through the paternal line. In contrast, a parent-of-origin effect was present for ADHD hyperactive-impulsive symptoms, with mothers', but not fathers', symptoms predicting daughters' symptoms, suggesting that girls may be more susceptible to the inheritance of ADHD through the maternal line (Goos et al., 2007). This may be explained by the role of sex-chromosomes or sex-specific physiological or hormonal factors (Goos et al., 2007). However, no parent-of-origin effect was found for parental inattentive symptom transmission, suggesting the two symptom domains in ADHD may show differential patterns of inheritance. This has indeed been recently reported in a meta-analysis

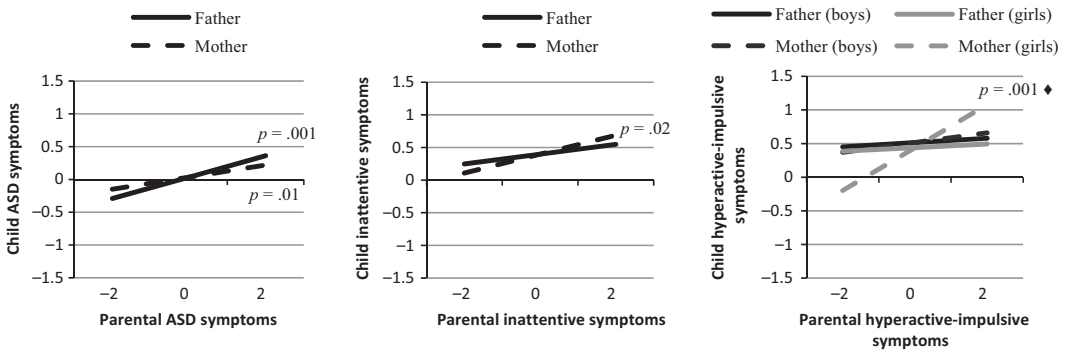

Figure 1 Illustration of parent-of-origin effects between parental and offspring pathology (*z*-scores)*. *Figures are not specified for gender, unless significant gender-interaction effects were found. Child ASD, ADHD inattentive, and hyperactive-impulsive symptoms as a function of the same symptoms in parents. Higher *z*-scores indicate more symptoms. ♦ Indicates a significant parent-of origin-effect

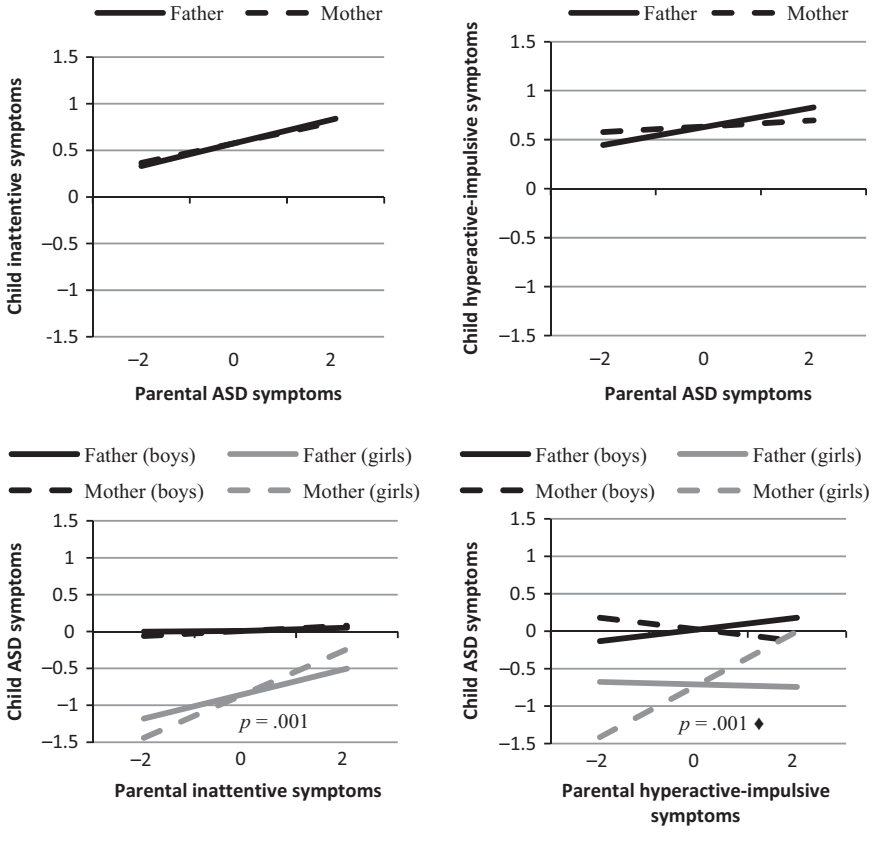

Figure 2 Illustration of cross-disorder parent-of-origin effects between parental and offspring pathology (*z*-scores)*. *Figures are not specified for gender, unless significant gender-interaction effects were found. Child ASD, ADHD inattentive, and hyperactive-impulsive symptoms as a function of cross parental symptoms. Higher *z*-scores indicate more symptoms. ♦ indicates a significant parent-of origin-effect

on twin studies: additive genetic factors may play a more substantial role in hyperactive-impulsive symptoms than they do in inattentive symptoms (the latter more strongly influenced by dominant genetic factors) and this difference is more pronounced in girls than in boys (Nikolas & Burt, 2010). In conclusion, these findings suggest preferential parental transmission does not play an important role in ASD, but may be of relevance in ADHD hyperactive-impulsive symptoms.

Of great interest are the results that contradict the thus far never studied hypothesis of cross-assortative mating for ASD and ADHD pathology. This suggests that children are unlikely to develop both disorders as a result of a 'double-whammy' effect in which two separate sets of risk genes, an ASD set from one parent and an ADHD set from the other parent, are carried over together at a higher frequency than expected by change. On the one hand, given the high correlations between ASD and ADHD pathology *within* parents, it may be suggested that parents transfer ASD/ADHD-common factors to their offspring, whose phenotypic expression may then depend on the parent-of-origin. On the other hand, this is contradicted by the selective effect of parental (mainly mothers') ADHD symptoms on

offspring ASD symptoms, but not the other way around. In other words, the risk for developing ASD in offspring is enhanced when parents score high on ASD and/or ADHD symptoms, whereas the risk for developing ADHD in the offspring is only enhanced when the parents score high on ADHD pathology. This may suggest that risk factors underlying ASD may overlap to a larger degree with risk factors underlying ADHD than vice versa. However, we realize we only have preliminary evidence to support this hypothesis, and further research which includes a pure ADHD group is needed to clarify this issue. As we found no evidence for cross-assortative mating, this may not explain the co-occurrence of ASD and ADHD. An alternative explanation for the co-occurrence of ASD and ADHD, besides the shared underlying etiology, could be that one of the disorders produces a phenocopy of the other. It is possible that a child has a strong genetic disposition for ADHD, but when growing up in an unhealthy parenting environment this could lead to ADHD based on the genotype and ASD symptoms based on the environment (Rommelse et al., 2010). However, more research in the area of the co-occurrence of both disorders is needed.

Our findings should be interpreted in the context of several limitations. First, we relied only on self-reports of parent behavior instead of using multiple informants. Parental psychopathology may have obscured the self ratings of problem behavior, resulting in an underestimated amount of symptoms and affected parents in our sample. Parents with, for example, ADHD tend to be more positive about their own behavior (Kooij et al., 2008; Young & Gudjonsson, 2005), perhaps due to limited self-awareness (Zucker, Morris, Ingram, Morris, & Bakeman, 2002). This would explain why the mean scores of ADHD hyperactive-impulsive symptoms in our sample were significantly lower than found in the general population, but is contradicted by the finding of increased ASD pathology in the sample. A second limitation is the possibility of informant bias, since parents reported both on their own symptoms and on the symptoms of their children. The non-significant results that were found when using only teacher's reports could be the consequence of medication use of the child at school, resulting in lower teacher scores. Nonetheless, it is important to confirm the findings of the present study through the use of multiple informants reporting about the ASD and ADHD symptoms of parents and children. A third limitation is that the child behavior questionnaires were completed mostly by mothers, therefore possibly providing a positive or negative informant bias. Though in that case, we would expect to find very different results for mother ratings than for father ratings, which was overall not the case.

In conclusion, our study suggests that there is no (cross-)assortative mating for ASD and ADHD. No parent-of-origin effects were found for both ASD and ADHD inattentive symptom transmission, though only maternal ADHD hyperactive-impulsive symptoms were predictive for daughters' hyperactive-impulsive symptoms. Parental ASD pathology was not predictive for offspring ADHD pathology, but mother's ADHD pathology was predictive for offspring ASD pathology even when corrected for maternal ASD pathology. The latter may suggest that risk factors underlying ASD may overlap to a larger degree with risk factors underlying ADHD than vice versa. However, future research is needed to clarify this issue.

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Key points

- (Cross-)assortative mating for ASD and ADHD does not form an explanation for the frequent co-occurrence of these disorders within families.
- A parent-of-origin effect was only present for ADHD hyperactive-impulsive symptoms of mothers predicting daughters hyperactive-impulsive symptoms.
- ASD pathology in parents was not predictive for ADHD pathology in the offspring, but mother's ADHD pathology was predictive for offspring ASD pathology.
- The results may suggest that risk factors underlying ASD may overlap to a larger degree with risk factors underlying ADHD than vice versa.

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